

Aus dem Kinderspital Basel

Direktor: Prof. Dr. A. Hottinger

Arbeit unter der Leitung von Prof. Hottinger

Transplacental varicella

A Report of 2 Cases

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde der medizinischen Fakultät
der Universität Basel

vorgelegt von

HYMAN GOLDMAN

von Montreal (Kanada)

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GENEHMIGT AUF ANTRAG VON PROF. DR. A. HOTTINGER

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TO MY PARENTS

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I. Introduction

The possibility of the transfer of disease intrauterine from mother to child has been steeped in the folklore and superstition of man for many centuries. Only in the air of scientific investigations of the last few generations has the problem been clarified as to the modes of passage and the extent and importance of these passages. In its wake, and as the result of the rapid advances made in bacteriology and immunology during this latter period, has come the further extension of this problem. This is the consideration of the immune bodies produced in the mother and their passage transplacentally to the child.

With the above in mind this paper will report on an additional two cases of the passage of disease, namely varicella, transplacentally from mother to child so as to expand the literature in relation to this problem. Further this paper will also attempt to show by compilation to what extent other pathological organisms have penetrated the placental barrier. Then, by the same token, this paper will also show how vast is the penetration of this barrier by the numerous immune bodies manufactured by the mother and passed passively to the foetus which then offers an early protection to the infant in the first few months post-partum.

II. Review of Literature

A review of the world literature shows that a case of congenital varicella was first reported by Hubbard (1) in 1878 and since then there have been an additional 24 cases reported. These infants manifested the disease from a period four days pre-partum (2) until three weeks post-partum (3) (18). Only those infants which showed the disease at three weeks of age or younger post-partum could be considered as possible bona-fide congenital varicella cases and so included in the above group. Since it is generally accepted by most authorities that the

incubation time can extend for as long as three weeks, those older than three weeks when first showing the lesions would be strongly suspect of having contracted the disease post-partum and so invalid for our above group.

Of the total 25 cases, there were six reported deaths, two of these being premature infants. The times of the deaths ranged from birth until three weeks of age. Some of the authors (9) (12) (13) reported as cause of death, "multiple necrotic areas with inclusion bodies in lungs, liver, stomach and the gastro-intestinal tract." The other authors made no mention of causes of death. Varicella complications very rarely lead to death and then only with encephalitis as the cause. Since there was a 25 per cent death rate reported and since varicella does not leave typically necrotic areas, one must suspect some other pathological organism, here perhaps *Listeria*. This disease entity has been found to cause multiple necrotic areas and has been reported to have lead to post-partum death in a few instances.

Age of Pat. when disease manifested itself	No. of cases	Alive	Died	Source
4 days pre-partum	1	1	0	(2)
At birth	6	5	1	(4) (5) (6) (7)
1 st day post-partum	2	2	0	(1) (5)
2 nd day "	1	1	0	(8)
5 th day "	1	1	0	(9)
8 th day "	4	3	1	(8) (10) (11) (12)
9 th day "	1	1	0	(13)
12 th day "	1	1	0	(14)
13 th day "	1	1	0	(15)
14 th day "	1	1	0	(3)
16 th day "	1	1	0	(3)
17 th day "	1	1	0	(3)
21 st day "	4	0	4	(3) (16)
Totals	25	19	6	

III. Review of the two cases

(a) Case No. 1

Ten days before delivery of her child, the mother manifested the typical varicella lesions. At delivery the child appeared normal, was 3500 gm and 50 cm long. There were no apparent skin lesions to be seen. Two hours post-partum the child first showed the typical varicella papules and vesicles which were distributed on both the hairless and hair containing parts of the head, on both arms and legs, on the foot soles and on the trunk. These efflorescences then took on the multistage picture of varicella with the formation of pustules and crust covered lesions. The child passed an uneventful disease period and was free of the lesions in a week and recovered completely.

Laboratory findings :—Lymphocytes 16 % – 49 %
Eosinophiles 1.5 % – 3 %
Wa.—

(b) Case No. 2

The pregnant mother manifested the first out-croppings of the typical varicella lesions two days post-partum. At birth the child was 4100 gm and 52 cm long and was free of any skin lesions. The child had an A/o blood incompatibility and was given an exchange transfusion to lower an indirect bilirubin level of 23.5 mg per cent. 16 days post-partum the child manifested the first signs of typical varicella multistage lesions with the efflorescences distributed mainly on the face and on the rump and legs. The child passed an uneventful disease period, and within 10 days was free of the crusts and declared completely healed.

Laboratory findings :—Wa. –
W.B.C. 17.900 – 9.200
Neutro 51 % – 20 %
Eosinophiles 13.5 % – 0.5 %
Lymphocytes 62 % – 25 %
Coombs –

IV. Differential diagnosis

The fact that the mothers contracted varicella in the period just before delivery with possible subsequent infection of the foetus must not rule out a careful differential diagnosis, for other disease processes could confuse the picture.

(1) *Dermatitis herpetiformis*

The lesions here are polymorph. with vesicles predominating and with a tendency of grouping of the lesions. There is an eosinophilie and a residual pigmentation, and a typical histological picture.

(2) *Lues*

The lesions are characteristically of Pemphigoid vesicles with a maculo-papulo eruption which is primarily found on the foot soles and palms of the hands. The Wassermann is positive. The child may also have other associated lesions at the time of birth such as a dirty pale-grey skin color, enlarged hard liver and spleen or a Rhinitis.

(3) *Herpes Zoster*

The lesions are characteristically one sided and show a segmented arrangement. The multiform lesions are less typical here. The appearance of pain before the manifestation of the skin lesions is also typical. After the lesions heal, a characteristic depigmented area remains.

(4) *Strophulus varicellousus*

The lesions are mainly in groups, and are found on the back and on the extensor sides of the extremities, and the head is left characteristically free. There is an associated itching and the blood picture is typical.

(5) *Strophulus*

The lesions are grouped and are mainly papulose, small, hard and pale red. The hair covered parts of head, the face and palms are typically free of lesions. There is associated itching and the blood picture is typical.

(6) *Scabies*

The lesions are typically mm. long thin stripped grooves and are found interdigitally, the wrist, elbows, rump and the area of the abdomen. The face is always free. With newborns the lesions are quite similar to the varicella efflorescences and only through the actual presence of the scabies can one be sure of its diagnosis.

(7) *Impetigo contagiosa*

The individual lesions are larger and appear to be in groups and the multistage character is less developed. There is more itching in the vesicle stage.

(8) *Variola*

There is a typical prodromal stage, with the eruption exanthema appearing at the same time of temperature fall. The lesions are not polyform but are all of the same stage namely the suppurative pustules, which has the typical central umbilication. The healed lesions leave typically a scar.

V. Discussion: - (of disease passage)

The central consideration for the passage of disease from mother to foetus is the role of the placenta. When a bacteraemia or viraemia occurs in the mother's circulation it has been shown conclusively that due to the intimacy of the placental circulation to the mother's the chorion is insufficient as a barrier. The pathological organisms, from the smallest viruses to the larger bacteria, seem capable of

enough penetrating power to break through into the foetal circulation. Once the break through has been made the foetus must contend with the consequences of a resultant generalized dissemination. If the breach is made in the early stages of pregnancy, the damage can be organopathic as has been shown in cases of rubeola (47) and in varicella (17) where multiple congenital defects result. Here the culprit can be the organism itself or some toxin thereof, and this problem remains to be settled. If the breach is made in the late stages of pregnancy the foetus can suffer a "normal" disease period completely intrauterine and be born with an active immunity against the disease. If the infection of the mother occurs close to parturition, then the foetus will manifest the disease process extra uterine as occurred in the above two cases. As the placental circulation becomes even more intimate in the 2nd half of the pregnancy, it would seem that the transplacental dissemination becomes much more likely then.

VI. Literature: - (on disease passage)

This permeability of the placenta has been observed in the case of Syphilis, Malaria (18), Leprosy (19), Pneumonia (20) and Gonococcus infections (21). Since children have been born with smallpox, measles and varicella (22) and experimental evidence shows a placental passage of rabies virus (23) (24), the viral passage seems to be beyond any doubt a reality.

A list will follow later which has been compiled from many sources and which indicates which organisms have been reported to have passed transplacentally.

VII. Discussion: - (of immune body passage)

The passage of immune bodies also considers the role of the placenta but the consideration does not stop here for the problem seems somewhat more complicated.

The new-born infant passes through a remarkable period, during its first six months of life, in which it is relatively immune to the ravages of numerous diseases to which an older child seems particularly susceptible to. These diseases coincide with the homologous immune bodies that the infant's mother has in her own blood and which she has actively produced when infected prior to her pregnancy. Therefore the infant in some manner acquires these immune factors from the mother. As early as 1911 Wegelius (25) attempted to consider all the possibilities of transference from mother to child to explain this acquired immunity. He considered:—

- (a) Hereditary transmission of the factors which produce immunity in the parents to the germ plasm so that these factors are maintained in the progeny of the future.
- (b) By the effect of agents which cause the reaction of immunity in the mother on the germ plasm or on the foetal organism —▷ active intrauterine transmission.
- (c) By the transmission to the foetus of the antibodies formed in the body of the mother —▷ passive intrauterine transmission.
- (d) By transmission of anti-bodies to the progeny whilst suckling.

The consideration of (a) involves those vague terms of “constitution” and “predisposition” of the child which although little understood are certainly factors of importance. This is shown by the fact that all other factors being equal there is a difference in disease susceptibility, receptibility, and of course, in different individuals. But the importance seems to be secondary here.

Factor (b) seems to be of a minor and isolated importance.

Since Wegelius' day factor (c) certainly has become the dominant means by which the child first acquires immunity. Since the immune bodies are intimate constituents of the mother's blood, one must

assume that these factors pass through the placental circulation during the diffusion exchange of $O_2 + CO_2$. The passive character of this immunity is shown by its transient nature although some other factor is involved for unlike passive immunity following an injection of serum which mainly lasts 3-4 weeks, that observed in the newborn infant lasts in the case of measles for five months, for scarlet fever 6-8 months and for diphtheria and polio equivalent times (22). An extensive literature exists showing conclusively the transmission of anti-bodies through the placenta, be they antitoxins, precipitins, bacteriolysins and complement fixing antibodies, and points to the relative importance of this mode of passage.

Factor (d) is also of some importance but certainly not dominant. Since colostrum contains a high content of globulin, which contains the immune bodies, Hottinger (26) states that the child can receive through the milk, diphtheria antitoxins measles "Schutzstoffe", staphylococcus antitoxine, Typhoid fever agglutinine and "bactericide stuff."

An additional fifth factor could be considered here. Although endometrial varicella has never been reported, it may be assumed that since varicella lesions are disseminated throughout the body, these lesions may also involve the endometrium with inoculation of the fetal membranes and the fetus. Therefore in the odd case one can make an assumption that in utero infection does not necessarily imply that fetal infection follows transplacental transmission.

VIII. Literature: - (on immune body passage)

Ehrlich (27) in his study of antitoxin immunity to ricin originally showed that passive transfer from immune mothers to their offspring occurs naturally. That antibodies were transferred through the placenta was shown by Park and Zingher (28) on diphtheria in which they compared Shick Tests on mothers and on infants and demonstrated that the newborn infants almost invariably gave the same Rx. as the

mothers. These observations were confirmed by Kuttner and Ratner (29) who worked with the Shick Test and made comparative titrations of the Antitoxin content of the maternal and cord blood. Park and Williams (30) concluded from these similar experiments that "if a mother has a bacterial infection disease and immunity develops she will transfer that immunity passively to her offspring. During late pregnancy if the mother herself has an infection disease there is a possibility that active immunity will develop in the fetus in utero." The placental transmission of diphtheria antitoxin has been established (32). The blanching of scarlet fever rashes with placental serums was found by Toomey in 79 per cent of 227 serums. The neutralization of polio virus by umbilical cord blood has been adequately demonstrated (33).

The passive immunity of the child to measles born of mothers who have experienced the diseases was shown (34) (35). Umbilical cord blood and blood of newborn infants contains *Staphylococcus* antitoxins in practically the same amounts as the maternal blood (36). Agglutinines against typhoid were found to pass the placenta by Schultz (37), Schumacher (38), Staubli (39), Mosse and Daunie (40) and by Peduzzi (41). It has been shown by Cooke (42) that the complement fixing antibodies of tuberculosis is transferred from mother to offspring. Aycock and Kramer (33) on the basis of neutralization tests conducted with serums of mothers and their offsprings, concluded that when the mother is immune to polio there is a passive immunity given to the infant through the placenta. This was shown again in cases of measles (43), in smallpox (44) and in diphtheria (45).

But one must keep in mind that the process of transplacental passage of factors from mother to child is not as simple and as automatic as one would be led to believe in the light of the above mentioned results. Problems of allergy are related to those of immunity and attempts to discover whether skin-sensitizing antibodies from the blood of the allergic mother may pass to the fetus and thus induce hyper-sensitiveness in the infant have given essentially negative results. So we see that the infant is born with an assortment of pas-

sively accepted antibodies against infection but escape a simultaneously acquired burden of undesirable antibodies of allergic significance (46). But this selective protection is far from exacting as witness the catastrophic results following the passing over of Rh. antibodies. The fact too that many constituents of the mothers blood have different concentrations from that of the infants' blood concentration shows that the passage of elements to the child through the placenta is not just a passive filtrative diffusion process but probably a more selective factor is operating.

IX. Compilation of reported transplacental passage

Disease	size (length) m μ	organism passes	antibody passes	antitoxin passes
Measles	?	X	X	
Polio	~ 12		X	
Varicella	150	X	X	
Vaccinia	175	X	X	
Smallpox	200-300	X	X (?)	
Rabies	~ 125	X		
Rubella	?	X	X	
Parotitis epid.	90-135	X	X	
Yellow fever	18-27	X	X	
Grippe	30-70	X		
Hepatitis epid.	?	X	X	
Herpes simplex	~ 125		X	
Scarlet fever	600-1000	X (toxin)	X	X
Diphtheria	1000-8000	X (toxin)	X	X
Pneumococcus	500-1250	X	X	
Infl. Bac.	~ 100	X	X	
Pneumonia	500-1250	X		
Gonococcus	600-1000	X		
Tetanus	4000-8000			X
Staphylococcus	800-1000			X
Typhoid fever	2000-3000	X	X (agglutin.)	
Malaria	1000-7000	X		
Toxoplasmosis	2000-6000	X	X	
Syphilis	6000-14000	X		
T.B.	500-4000	X	X	
Leprosy	1000-8000	X		

X. Discussion of the two reported cases

One must assume that since most women have had varicella, the occurrence of this disease in their young infants is theoretically unlikely in the light of the passive immunity given them. If however, the mother has never had varicella then the infant lacks the passive

immune bodies and may contract the disease soon after birth or even before birth. Pridham (2) observed a case of an infant born with varicella lesions that were typical of 4 day old lesions.

In case No. 1, there leaves no doubt, since the mother had the lesions 10 days before delivery, and the infant showed them two hours post-partum, that the disease was passed transplacentally at some time from the first exposure of the mother until a period ten days pre-partum.

In case No. 2, the time of contraction of the disease is open to question so therefore the possibility of either a transplacental or a post-partum infection cannot be definitely established. Each is likely. Since the child first showed the lesions 16 days post-partum and since it is recognized that the incubation time may extend for as long as three weeks before lesions will show it is entirely possible that very shortly before parturition the virus passed transplacentally to the foetus. Again it is also possible that in its passage through the birth canal the infant could have been infected by contiguity with some infected tissue of the canal. And again it is quite possible that although the mother had contracted the disease whilst the foetus was still in utero, the virus did not pass the placenta and instead the infant contracted the disease from the mother post-partum. Some interesting questions arise in this case. Could the infection of the child have been passed through the donor's blood given to the infant in the exchange transfusion? Also, did the donor have immune bodies to the varicella and if so why did they not abort the disease?

Of course, in both cases since varicella contracted a second time is extremely rare, one must assume that the two mothers had no previous history of varicella, manifested or abortive. They therefore lacked the immune bodies to give themselves protection against the disease and also to pass these same bodies on to their offspring and so endow them too with protection.

Summary

Two cases of congenital varicella were reported, one infant manifesting the disease two hours post-partum and the second infant 16 days post-partum. The transplacental passage of disease and their immune bodies was considered in relation to the possibilities of the above two cases occurring.

Zusammenfassung

Es wird über zwei Fälle von kongenitaler Varicella berichtet, wobei die Erkrankung bei einem Kind zwei Stunden und beim zweiten 16 Tage post partum manifest wurde. Die Möglichkeiten einer transplacentaren Passage der Krankheit und ihrer Immunkörper wird anhand der beiden oben beschriebenen Fälle diskutiert.

Résumé

Rapport consacré à deux cas de varicelle congénitale, l'un s'étant déclaré deux heures, l'autre seize jours après la naissance. L'auteur envisage à ce propos la possibilité d'un passage transplacentaire de la maladie et de ses immunisines.

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Curriculum vitae

I was born April 3, 1927 in Montreal, Canada where I completed my primary schooling in 1940 and my high school education in 1945.

After an interval of three years, part of that in the armed forces, I immatriculated into the natural sciences department of the University of Illinois. Except for one year, when I attended McGill University in Montreal, I completed my Baccalaureate education at Illinois in 1952 with a Bachelor of Science Degree. I then devoted a year of post-graduate work in Psychology at Illinois.

I immatriculated into the University of Fribourg in 1953 and there passed my 2nd propaedeutic examination in 1955.

I spent my first two clinical semesters at Lausanne and then transferred to Basle where I completed my medical studies with the Staatsexamen in November 1958.

